Citation:

Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med*. 2002; 346 (15): 1,113-1,118.

PubMed ID: 11948270

Study Design:

Prospective nested case control

Class:

C - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To investigate whether blood levels of long-chain n-3 PUFA are associated with reduced risk of sudden death in those without a history of cardiovascular disease.

Inclusion Criteria:

Apparently healthy men in the Physicians' Health Study (male physicians, 40 years to 84 years old in 1982).

Exclusion Criteria:

No history of MI, stroke, transient ischemic attacks or cancer.

Description of Study Protocol:

- *Baseline:* Questionnaire on health status and CVD risk factors, blood samples
- *12 months:* Dietary intake of fish ascertained in shortened FFQ
- *Six months:* CVD information updated
- *One year and annually for 17 years:* CVD information updated.

Data Collection Summary:

- Fatty acid composition of previously-collected blood was analyzed by gas-liquid chromatography
- Analyzed in groups of three blinded samples.

Description of Actual Data Sample:

- Over 17 years of follow-up, 201 sudden deaths from cardiac causes were documented. 119 of these had a baseline blood sample available. 94 had been free of confirmed CVD before death.
- 94 subjects were matched with two control subjects (age within one year, smoking status, length of time since randomization).

Summary of Results:

Significantly lower levels of long-chain N-3 fatty acids were found among current smokers than among former smokers or those who had never smoked (mean, 4.47±1.31% vs. 5.20±1.30% of total fatty acids; P=0.002). In addition, the baseline blood level of long-chain N-3 fatty acids was significantly correlated with fish intake at 12 months (R^2=0.24, P=0.001).

The mean level of total long-chain N-3 fatty acids was significantly lower among the men who died suddenly than among the controls (4.82±1.31% vs. 5.24±1.32% of total fatty acids, P=0.01). In contrast, the levels of the other fatty acids, including the short-chain N-3 PUFA (a-linolenic acid), SFAs, MUFAs, N-6 PUFAs and trans-unsaturated FAs, did not differ significantly between men who died suddenly and controls.

Baseline blood levels of long-chain N-3 fatty acids were inversely related to the risk of sudden death both before adjustment for age and smoking status (P or trend =0.004) and after such adjustment (P for trend =0.007). As compared with men whose blood levels of long-chain N-3 fatty acids were in the lowest quartile (3.58% total FAs), the relative risk of sudden death was significantly lower among men with levels in the third quartile (adjusted relative risk, 0.28; 95% CI, 0.09 to 0.87) and the fourth quartile (6.87% total FAs) (adjusted relative risk, 0.19; 95% CI, 0.05 to 0.71).

Author Conclusion:

- In this prospective nested case-control study, the baseline blood level of long-chain N-3 fatty acids was inversely associated with the subsequent risk of sudden death, even after known confounders had been controlled for. The association was linear, with a statistically significant inverse trend across quartiles of levels of long-chain N-3 fatty acids.
- As compared with men with levels of long-chain N-3 fatty acids in the lowest quartile, those with levels in the highest quartile had an 81% lower risk of sudden death. This relationship persisted when blood levels of other fatty acid groups were controlled for in the model. Therefore, the association did not appear to depend on compensatory changes in the levels of other fatty acids.
- In summary, these prospective data suggest that the long chain N-3 fatty acids found in fish may reduce the risk of sudden death from cardiac causes, even among men without a history of CVD.

Reviewer Comments:

- *Interesting that dietary fish intake was ascertained and that subjects were matched with two controls*
- *Authors note limitations of analyses based on a single baseline measurement, which would not accurately reflect levels of long-chain N-3 fatty acids over long periods.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	No
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	No
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes

3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	No
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	Yes
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes

6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	Yes
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes

8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes